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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,674	11/13/2003	Ken Y. Lin	STAN-276	9855

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EXAMINER	
VENCI, DAVID J	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/713,674	LIN & COOKE	
	Examiner	Art Unit	
	David J. Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. §.133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *August 8, 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,15 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,15 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges Applicants' reply, filed August 2, 2006, which amends claims 1 and 5, and cancels claim 16.

Currently, claims 1-9, 15 and 17-19 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112 – first paragraph

Claims 1-9, 15 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Independent claim 1 recites, *inter alia*, a method of detecting asymmetric dimethylarginine (ADMA) in a sample comprising ADMA and at least one of symmetric dimethylarginine (SDMA) and arginine. In step (a), an α-dicarbonyl compound is used to chemically modify SDMA and arginine. Thereafter, in step (b), ADMA is detected.

According to paragraph [0048] of Applicants' specification, a sample[1] is subject to SPE extraction, derivatization with *o*-phthaldialdehyde in the presence of methanol, borate and 3-mercaptopropionic acid (see para. [0048]). According to paragraphs [0034] and [0098] of Applicants' specification, an α-dicarbonyl compound (*e.g.*, phenylglyoxal dissolved in water, pH 9.0) is added to a sample, and a reaction is allowed to proceed anywhere from 15 seconds to 2 hours in the dark at room temperature. The reaction is performed with anywhere from 0.1 mM to 50 mM of α-dicarbonyl compound (see para. [0033]). Applicants' specification contemplates one "modified SDMA" phenylglyoxal derivative (see Fig. 4) and one "modified arginine" phenylglyoxal derivative (see Fig. 2).

Applicants' specification does not describe a two-step method comprising the steps of: a) contacting a sample with an α-dicarbonyl compound, followed by b) detecting ADMA in the sample. Applicants' specification does not describe the exact experimental conditions for performing said two-step method comprising the steps of: a) modifying SDMA and arginine, followed by b) detecting ADMA in the sample. Applicants' specification does not describe the exact reaction conditions for reacting a sample with an α-dicarbonyl compound, resulting in detectable ADMA. Applicants' specification does not describe a detecting means capable of detecting ADMA in the product of a reaction between a sample with an α-dicarbonyl compound. Other than phenylglyoxal derivatives (see Figs. 2 and 4), Applicants' specification does not contemplate any other "modified SDMA" derivatives or "modified arginine" derivatives.

According to the decision in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), the factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include:

(A) The breadth of the claims;

[1] The term "biological sample" encompasses a clinical sample, and also includes cells in culture, cell supernatants, cell lysates, serum, plasma, cerebrospinal fluid, urine, saliva, biological fluid, and tissue samples. See specification,

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Here, the breadth of independent claim 1 is extremely broad. Claim 1 generically encompasses a method of detecting ADMA in any "sample", using any "α-dicarbonyl compound" and any "detecting" means. Claim 1 does not specify whether/what sample clean-up steps may be required. Claim 1 does not specify any experimental parameters for carrying out the derivatization reaction.

The state of the prior art appears to recognize a high degree of unpredictability in the field of arginine chemical derivitization. For example, Baburaj *et al.*, 1199 BIOCHIM. BIOPHYS. ACTA 253 (1994), discovered two α-dicarbonyl compounds (see Title, "HOCGO" and "DMACGO") that produced unexpected, unpredictable results when used to derivatize samples. Specifically, Baburaj *et al.* discovered that HOCGO and DMACGO are: (1) capable of reaction with cysteine and lysine residues (in addition to arginine); (2) extremely sensitive to variations in solvent pH and polarity; (3) capable of reacting with samples that don't possess arginine; and (4) react with samples non-covalently (see p. 262, right column, Section 4.2). With respect to HOCGO and DMACGO, the findings of Baburaj *et al.* suggest that the ability of α-dicarbonyl compounds to distinguish between ADMA-containing samples versus non-ADMA containing samples may be somewhat limited using fluorescence-based detection.

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paragraph [0016].

According to Schwarzenbolz *et al.*, 205 Z. LEBENSM. UNTERS FORSCH. A 121 (1997), under certain reaction conditions, the α-dicarbonyl compound, glyoxal, produces two arginine derivatives (see Fig. 3). Similarly, Sopio & Lederer, 201 Z. LEBENSM. UNTERS FORSCH. A 381 (1995), teaches that, under certain experimental conditions, the α-dicarbonyl compound, deoxyosones, results in two tautomeric products (see Fig. 6). Based on Applicants' limited disclosure, whether these and other derivatives are contemplated, and whether these derivatives are distinguishable from ADMA is not clear.

Applicants' specification provides inadequate direction for carrying out the arginine derivatization reaction on "a sample." Paragraphs [0034] and [0098] of Applicants' specification provides the extent of direction, disclosing that an α-dicarbonyl compound (*e.g.*, phenylglyoxal dissolved in water, pH 9.0) is added to a sample, and a reaction is allowed to proceed anywhere from 15 seconds to 2 hours in the dark at room temperature. Examiner posits that the level of direction provided in paragraphs [0034] and [0098] of Applicants' specification is insufficient to enable persons of ordinary skill to perform a two-step method of detecting ADMA comprising the steps of: a) contacting a sample with an α-dicarbonyl compound, followed by b) detecting ADMA in the sample. The working examples located on pp. 22-25 of Applicants' specification are inadequate for similar reasons.

Given the aforementioned deficiencies in Applicants' disclosure, Examiner posits that the quantity of experimentation needed to perform the claimed two-step method of detecting ADMA is undue.

Claim Rejections - 35 USC § 112 – second paragraph

Claims 1-9, 15 and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1:

The phrase "said sample comprises ADMA and at least one of SDMA and arginine" is indefinite. The phrase appears inconsistent with the preamble phrase "a sample comprising ADMA, symmetric dimethylarginine (SDMA), and arginine".

In claim 1, the passive voice recitation "said modified SDMA and said modified arginine are distinguishable" is indefinite. The identity of object(s) and/or step(s), if any, required for performing distinguishing is not clear.

Response to Arguments

In prior Office Action, claims 1-9 and 15-19 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

In response, Applicants argue

1. The specification provides ample description of the claimed method (see Applicants' reply, paragraph bridging pp. 5-6; p. 6 first full paragraph).
2. The specification provides ample description of methods for detecting ADMA (see Applicants' reply, p. 6, second full paragraph).
3. The specification contemplates use of any of a variety of α-dicarbonyl compounds (see Applicants' reply, p. 6, third full paragraph).
4. The cited art does not support a conclusion of lack of enablement (see Applicants' reply, p. 6, last paragraph).

Applicants' arguments have been carefully considered but are not persuasive.

With respect to 1), 2) and 3), Examiner acknowledges that the specification literally recites a procedure involving steps of (a) contacting a sample with an α-dicarbonyl compound; and (b) detecting ADMA. In addition, Examiner acknowledges that the specification literally recites laundry lists of α-dicarbonyl compounds, reaction concentrations, reaction times and reaction temperatures.

However, despite Applicants' disclosure of the aforementioned information, Applicant's disclosure does not describe the claimed two-step method because Applicant's disclosure does not describe any experiment involving the claimed two-step method comprising the steps of: a) modifying SDMA and arginine, followed by b) detecting ADMA in the sample. Examiner posits that the mere listing of α-dicarbonyl compounds, reaction concentrations, reaction times and reaction temperatures does not

amount to a two-step method absent a teaching of how to incorporate the information contained within each list into a working two-step method. Furthermore, Applicants' specification is not suggestive of a two-step method. According to paragraph [0048] of Applicants' specification, a sample is first subjected to SPE extraction, derivatization with *o*-phthaldialdehyde in the presence of methanol, borate and 3-mercaptopropionic acid (see para. [0048]).

More importantly, Applicants' specification does not describe a detecting means capable of detecting ADMA in the product of a reaction between a sample with an α-dicarbonyl compound. Applicants' reply alludes to spectrophotometric, immunoassay, HPLC and/or capillary electrophoresis detecting means (see Applicants' reply, p. 6, second full paragraph). However, Examiner posits that the mere listing of various detecting means does not amount to a two-step method absent a teaching of how to incorporate each one of the detecting means into a working two-step method.

With respect to 4), Examiner acknowledges Applicants' position that "[a]ll that is required is that the α-dicarbonyl compound modify any SDMA and any arginine that may be present in the sample, and that the α-dicarbonyl compound not modify ADMA" (see Applicants' reply, p. 7, bold text). However, Applicants' mere pronouncement of such does not cause Applicants' specification to be enabled for such.

In the instant and prior Office Actions, Examiner sets forth three examples from the prior art that suggest Applicants' potentially overly-simplified two-step method will not perform as intended to detect ADMA. Specifically, Baburaj *et al.*, 1199 BIOCHIM. BIOPHYS. ACTA 253 (1994), disclose a fluorescence-based detection system that would not distinguish ADMA because the disclosed α-dicarbonyl compounds are: (1) capable of reaction with cysteine and lysine residues (in addition to arginine); (2) extremely sensitive to variations in solvent pH and polarity; (3) capable of reacting with samples that don't possess arginine; and (4) react with samples non-covalently (see p. 262, right column, Section 4.2). Similarly, Schwarzenbolz *et al.* and Sopio & Lederer disclose α-dicarbonyl compounds that may not distinguish

ADMA because the disclosed α-dicarbonyl compounds produce multiple, unexpected arginine derivatives.

Applicants' reply repeatedly states that each of the α-dicarbonyl compounds disclosed by Baburaj *et al.*, Schwarzenbolz *et al.* and Sopio & Lederer are capable of reacting with arginine, which "supports the fact that the instant claims are enabled" (see Applicants' reply, p. 7, the last sentences of paragraphs 1, 2 and 5). However, it is not clear to Examiner how the antecedent (*i.e.*, each of the α-dicarbonyl compounds are capable of reacting with arginine) leads to the consequent (*i.e.*, the instant claims are enabled). Additional clarification addressing and resolving the issues set forth in the instant and prior Office Actions is necessary.

Conclusion

No claims are allowed at this time.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David J Venci
Examiner
Art Unit 1641

djv

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